



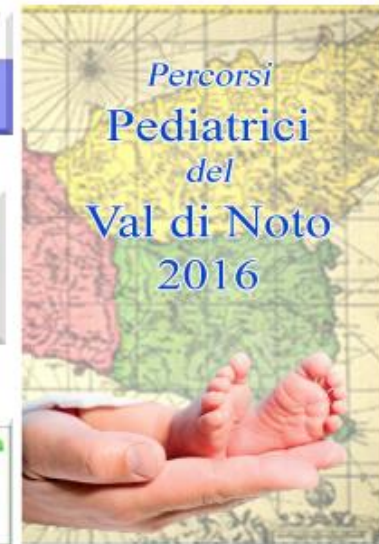
Dipartimento di Patologia Umana dell'Adulto e dell'Età Evolutiva  
«Gaetano Barresi»

**L'acne :**  
**dall'infanzia**  
**all'adolescenza**

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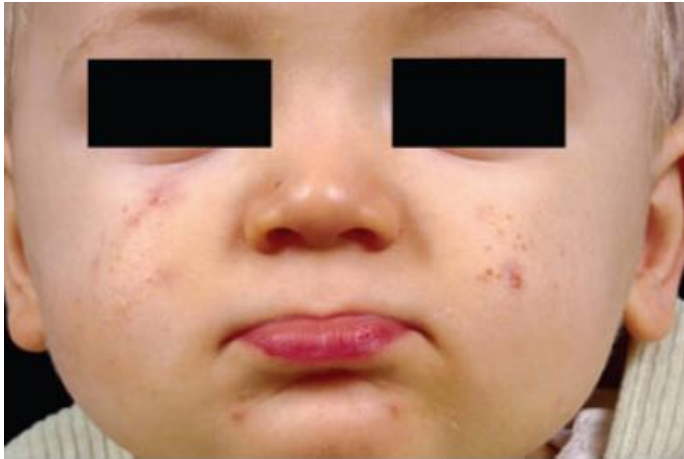


# ***Neonatal Acne***



- NA occurs in up to 20% of newborns.
- this is usually not true acne but rather neonatal cephalic pustulosis (NCP)
- the clinical importance of NA lies in its differentiation from infectious diseases, the exclusion of virilization as its underlying cause.
- NA must be distinguished from acne that is induced by application of topical oils and ointments (acne venenata) and from acneform eruptions induced by acnegenic maternal medications such as hydantoin (fetal hydantoin syndrome) and lithium.
- NA is due to an *increased sebum excretion and colonization by Malassezia species.*
- NA is generally a transient condition and treatment is usually not needed, topical ketoconazole 2% cream twice daily for 1 week has been used effectively

# ***Infantile Acne: A Retrospective Study of 16 Cases***



*Infantile acne (IA) is a rare disorder,*

*Predominance of male patients,*

*Average age at appearance of lesions (6–13 months),*

*Localization of the lesions predominantly on the cheeks, polymorphic nature :  
inflammatory and noninflammatory lesions.*

*Average duration (usually resolved by 3 years).*

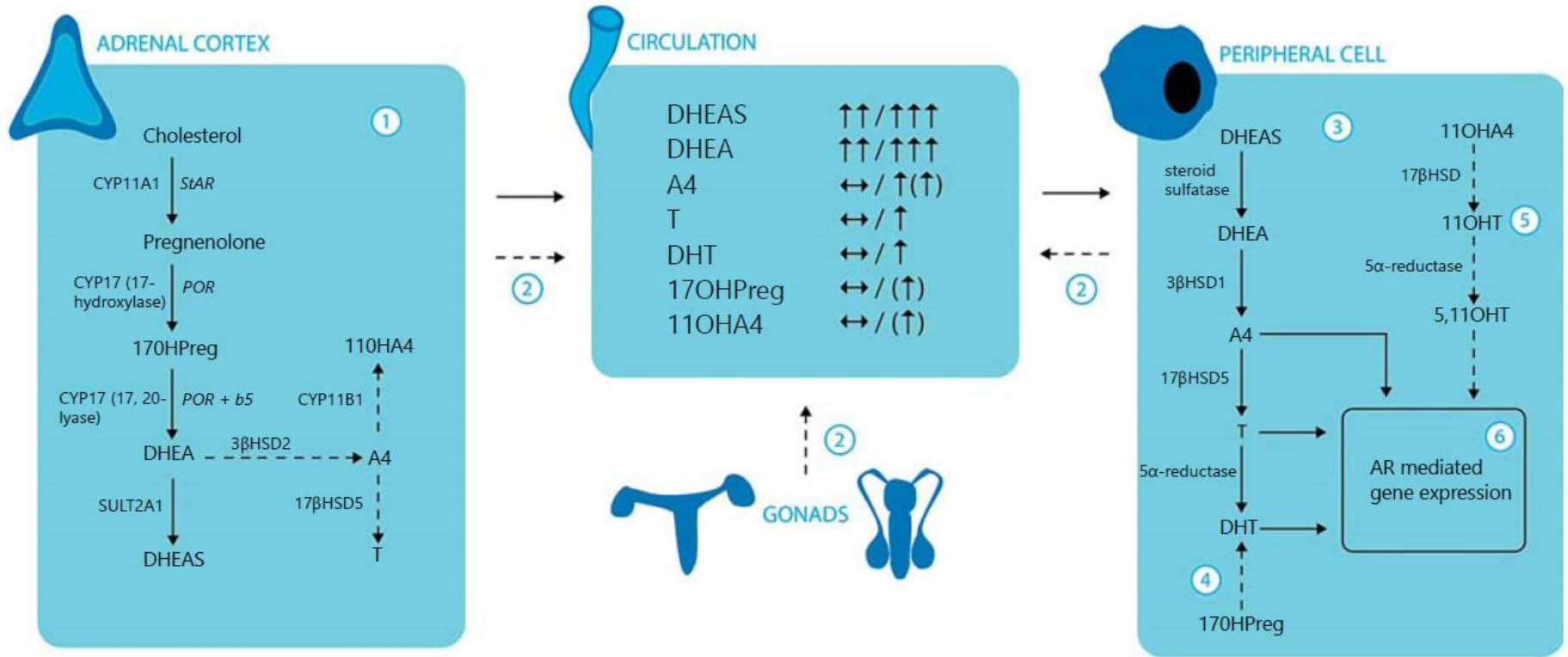
*IA is rarely associated with endocrinopathy/ iatrogenic origin*

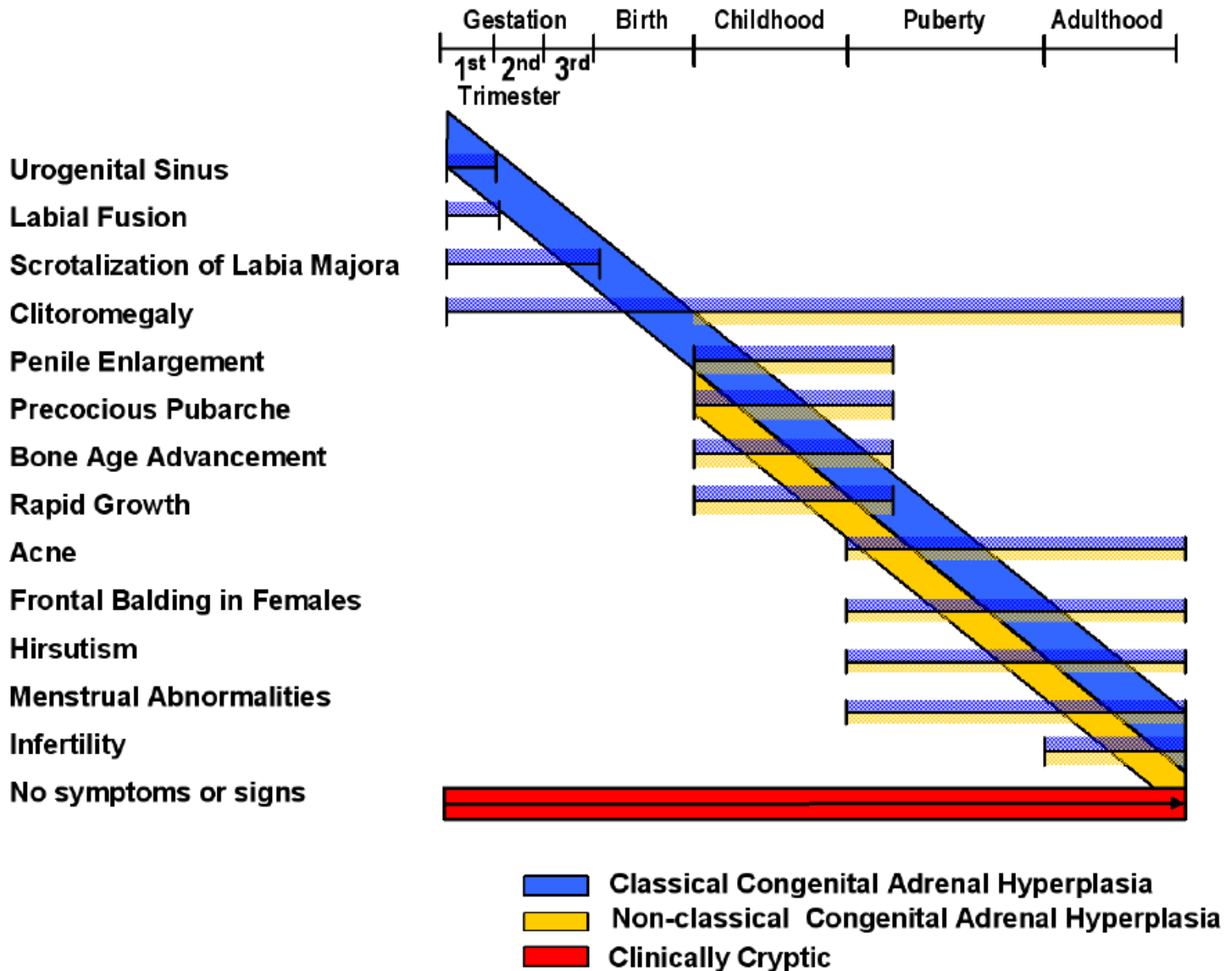
*Topical therapies such as benzoyl peroxide, retinoids, or antibiotics can be used*

# **Mid-childhood acne**

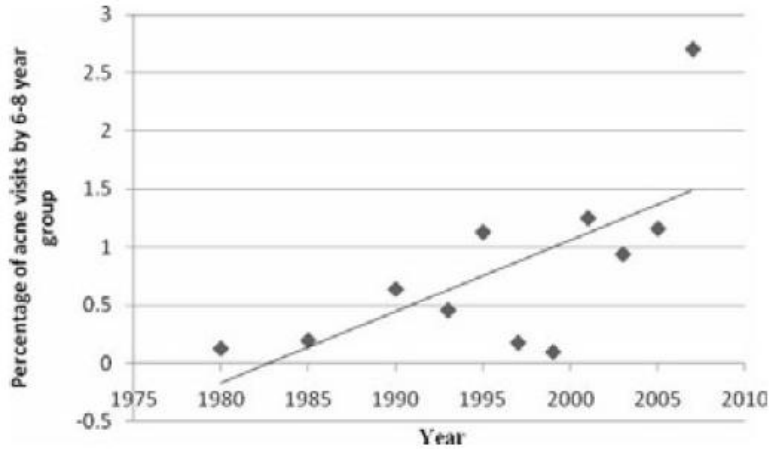
- *It occurs between 1 and 7 years of age,*
- *Acne during this period is rare, and the differential diagnosis can include angiofibromas, corticosteroid-induced acne, demodicosis, molluscum contagiosum and flat warts (verruca plana).*
- *True acne in these children should raise the suspicion for hyperandrogenism (premature adrenarche).*
- *This is a diagnosis of exclusion and congenital adrenal hyperplasia (CAH), central precocious puberty, exogenous androgen absorption, gonadal or adrenal tumors, and Cushing's syndrome.*
- *Initial assessment of these patients should include detailed history, family history, height, weight, body mass index, blood pressure measurement, and Tanner staging.*
- *diagnostic work-up can include serologic evaluation of serum total and free testosterone, dehydroepiandrosterone (DHEA) and/or DHEAS, 17 $\alpha$ -hydroxyprogesterone, cortisol, LH, FSH, and prolactin and radiologic bone age measurement.*

# Premature Adrenarche – A Common Condition with Variable Presentation



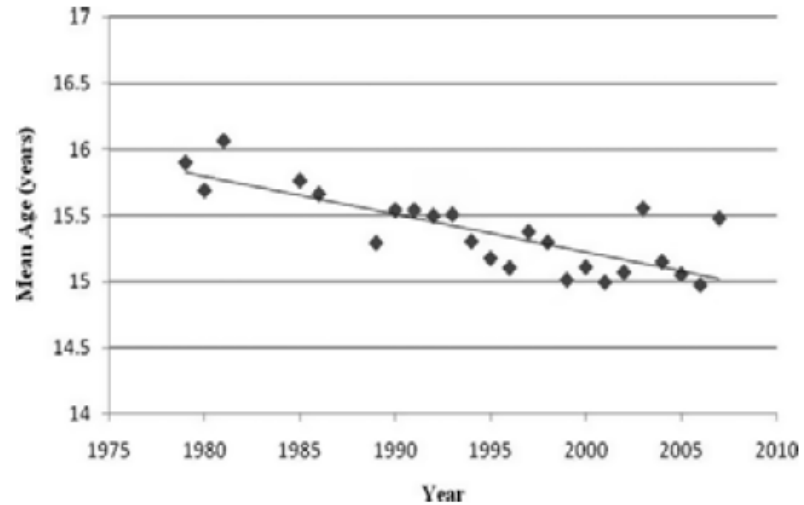


# ***Changing Age of Acne Vulgaris Visits: Another Sign of Earlier Puberty?***



*Percentage of physician visits by children seeking treatment for acne aged 6 to 8*

*Mean age of children seeking treatment for acne aged 6 to 18 according to year, 1979–2007*

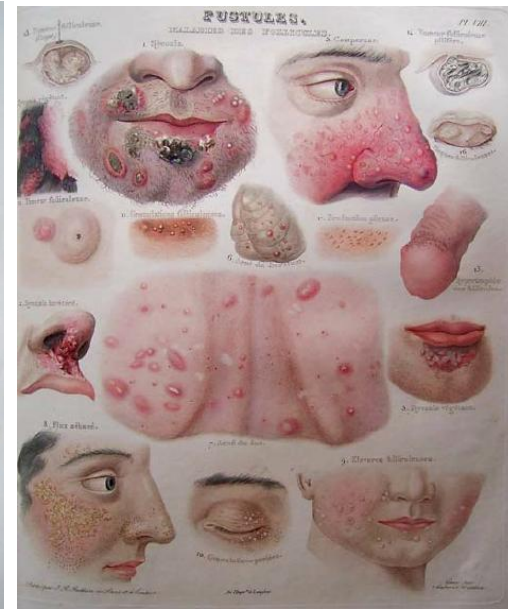




# Acne Pathogenesis: History of Concepts



Coll. bibliothèque Henri-Feulard, Hôpital Saint-Louis, Paris.



Dermatology 2014;229:1-46

*The word 'acne' was probably employed for the first time in the 6th century by Aetius Amidenus, physician in Constantinople who named 'ionthos' (ιονθωξ,) or 'acnae' the lesions occurring on the face at the 'acme' of life, i.e. puberty*

*Another explanation recalled by Grant suggests that acne was so called due to the absence of pruritus. In this hypothesis, acne would derive from the Greek letter α as a prefix to a contraction of a κνησις meaning 'scratching'.*

*A third hypothesis Grant regarded as less tenable suggests that αχνη, 'acne', means 'anything that comes off the surface'.*



# Acne

- *E' una dermatosi infiammatoria del follicolo pilo-sebaceo;*
- *Più frequente nel periodo dell'adolescenza (30-70%);*
- *Picco di incidenza 14-17anni nelle femmine;*
- *“ “ 16-19 anni nei maschi;*
- *Familiarità (uno e entrambi i genitori);*
- *Localizzazione prevalente al volto, ma anche al dorso e torace;*
- *Storia naturale: remissione spontanea dopo i 25anni.*

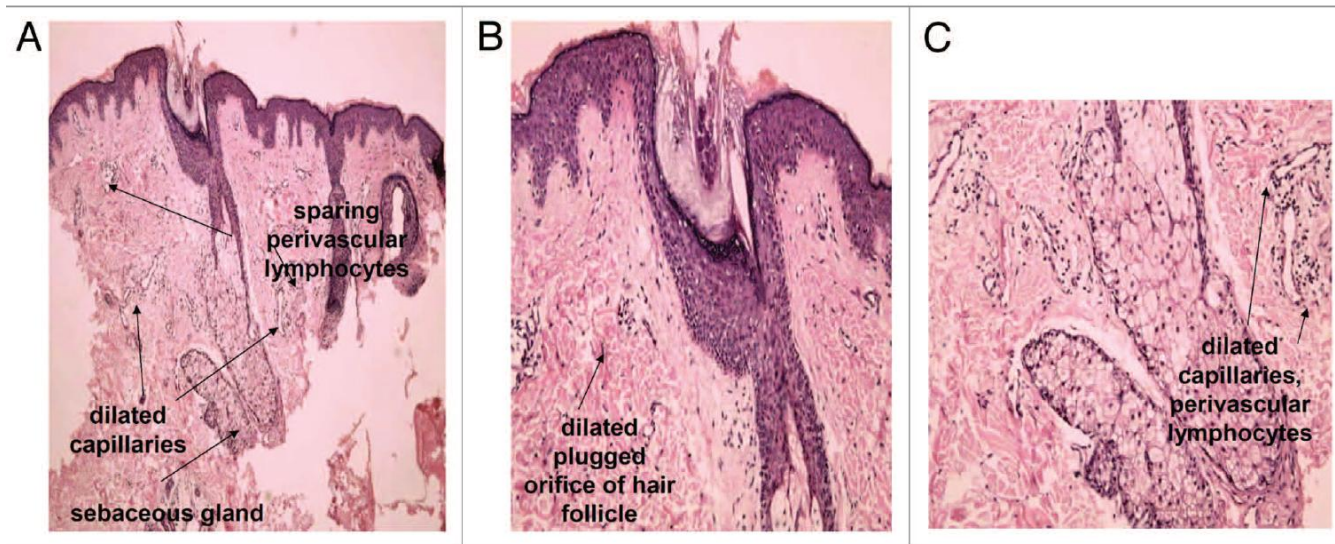
## Acne as chronic disease using the WHO criteria

Aspect	Acne
Major feature	Inflammation
Duration	>3 months to 10–30 years
Genetic background	+, long course, polygenic
Age of onset	circa 10 years
Spontaneous remission	> 80% (3 <sup>rd</sup> decade)
Recurrences	Common
Follow-up	At intervals/over years
Therapy	Long-term/ with pauses
Social counselling	+
Psychological counselling	Important
Scarring Anatomic Psychological	 + +

# ***Seborrhea and Acne: Inseparable Players of the Pathogenic Process***

- *The patients with acne had seborrhea, and the severity of the disease was related to the rate of the sebum excretion.*
- *Acne is due to the interaction between an increased rate of sebum secretion and a second factor that might be a greater resistance to sebum flow or an increased viscosity: increase in lipid cell production and increase in sebaceous gland size.*
- *Increased sebum excretion, alteration of lipid composition and the oxidant/antioxidant ratio characteristic of the skin surface lipids are major concurrent events associated with the development of acne.*

# ***An update on the role of the sebaceous gland in the pathogenesis of acne***



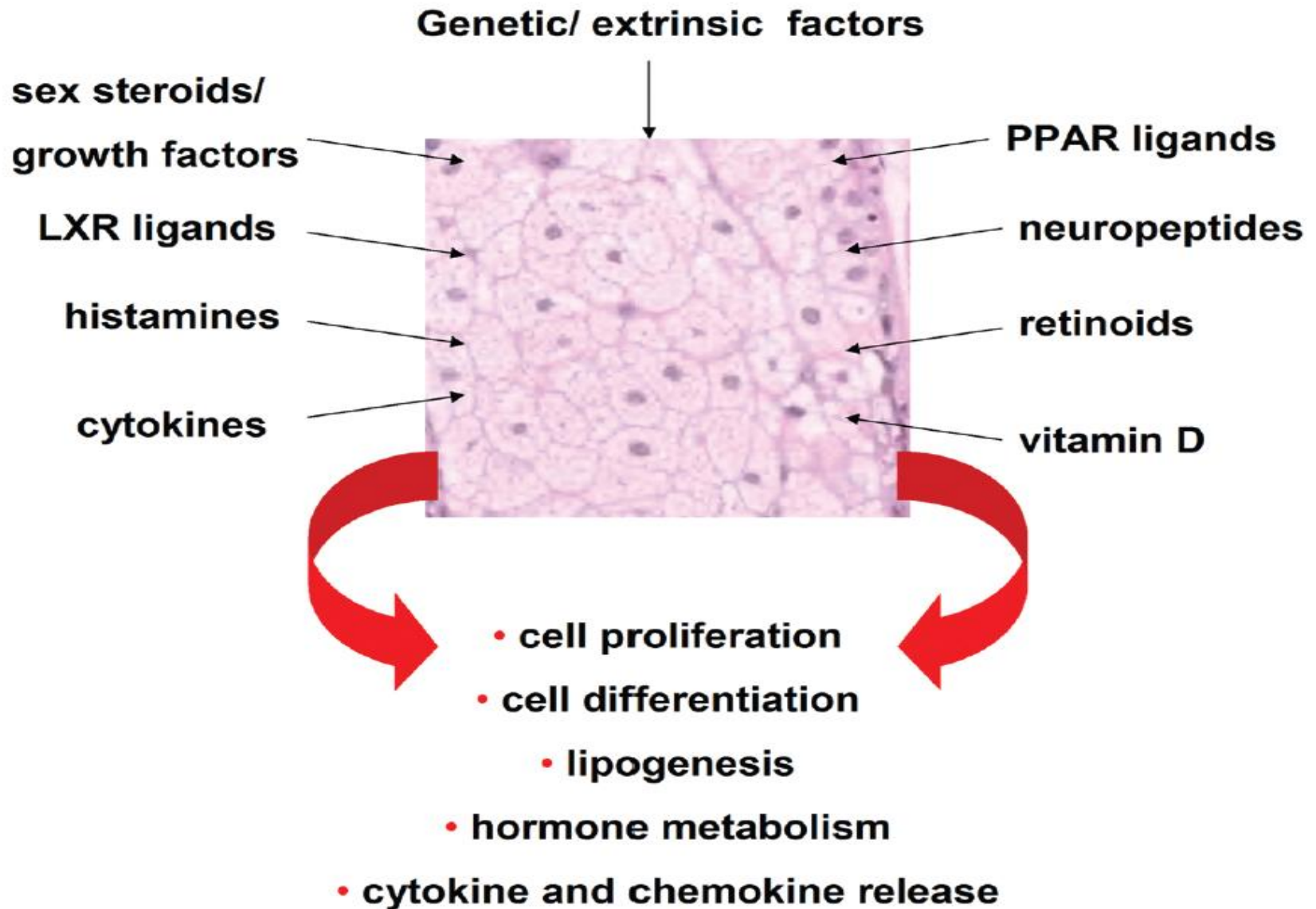
*low levels of linoleic acid*

*Elevated serum insulin and insulin-like growth factor-I (IGF-I) levels*

*peroxidation of squalene and a decrease in the level of vitamin E, the major sebum antioxidant*

*lipoperoxides and monounsaturated fatty acid (MUFA) are capable of inducing alteration in keratinocyte proliferation*

*Peroxides are capable of inducing production of pro-inflammatory cytokines and activation of peroxisome proliferator-activated receptors (PPAR)*



*Regulation of the biological function of human sebaceous gland cells.*

*Schematic overview. [LXR: liver X receptors, PPAR: peroxisome-proliferator activated receptors].*

# ***Effects of Hormones on Sebaceous Gland Cells***

## ***Sex steroids***

- *there is an association between local overproduction of active androgens and acne. Acne patients produced higher rates of testosterone and 5 $\alpha$ -dihydrotestosterone (5 $\alpha$ -DHT) in their skin than healthy individuals.*
- *High testosterone levels have been implicated with enhanced sebaceous gland activity in humans*
- *The effects of testosterone and 5 $\alpha$ -DHT are mediated by binding to the nuclear androgen receptor (AR), also expressed in human sebaceous gland cells*



## ***Growth factors***

- *increased sebum production peaks in mid-adolescence at a time that GH and IGF-I reach their highest serum levels*
- *in human skin the strongest expression of IGF-I protein has been found in maturing sebocytes and suprabasal cells of sebaceous ducts.*
- *in humans, IGF-I plays a key role in the induction of lipid synthesis in human sebocytes*

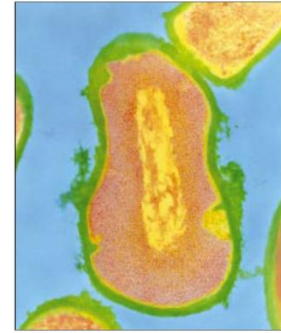
# ***Effects of NPs on Sebaceous Gland Cells***

- *NP are a heterogeneous group of biologically active peptides that are present in neurons of both the central and peripheral nervous systems*
- *human skin and in particular the human sebaceous gland has been shown to express functional receptors for NP, such as corticotropin-releasing hormone (CRH), melanocortins,  $\beta$ -endorphin, vasoactive intestinal polypeptide, neuropeptide Y and calcitonin gene-related peptide.*
- *These receptors modulate the production of inflammatory cytokines, proliferation, differentiation, lipogenesis and androgen metabolism in human sebocytes*

# ***Inflammation, Sebaceous Gland Cells and Acne***

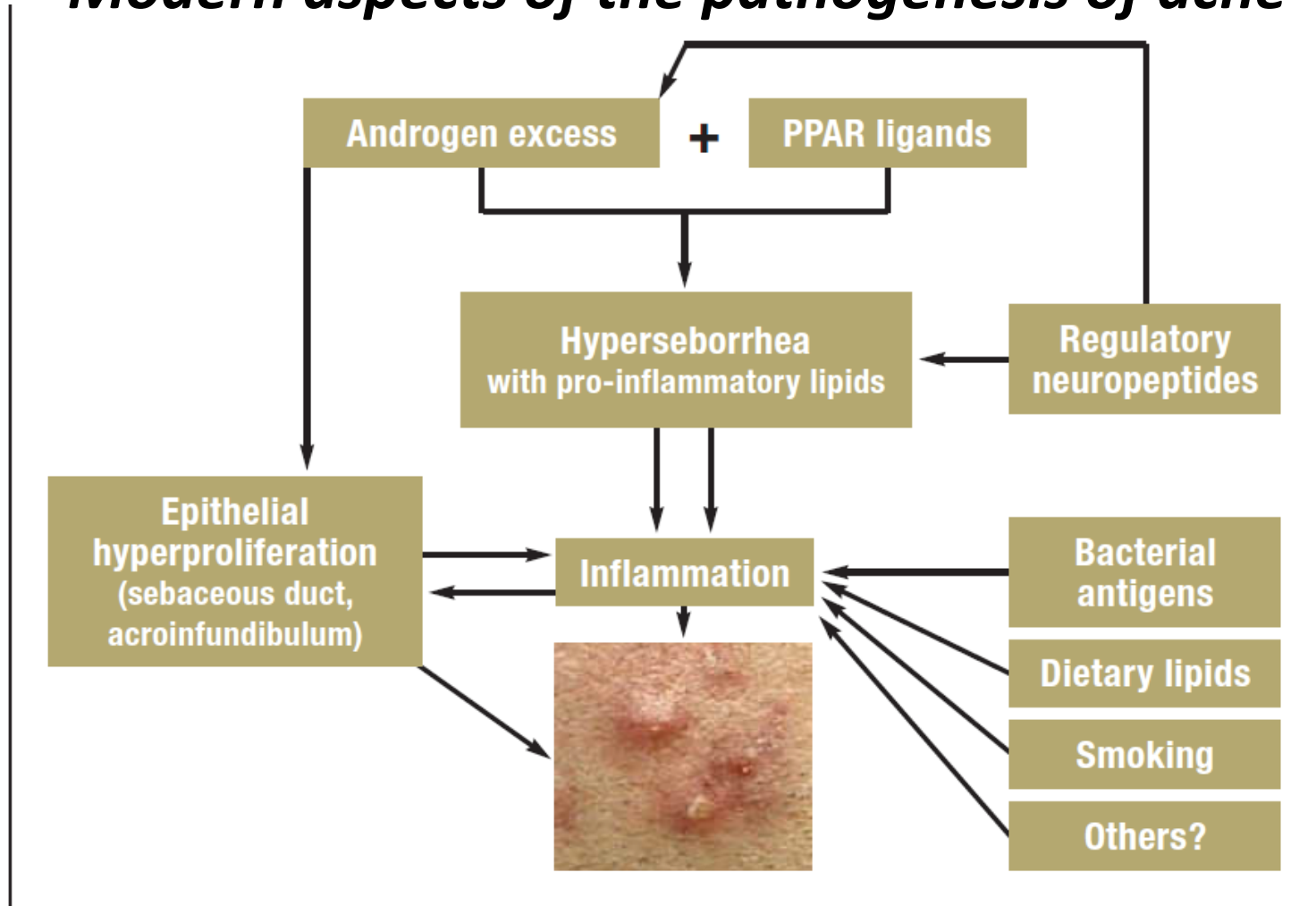
- *increase in IL-1 activity occurs before the hyperproliferation around uninvolved follicles and this triggers the activation of the keratinocytes.*
- *NFκB, a transcription factor critical for upregulation of many proinflammatory cytokine genes has been shown to be activated in acne lesions.*
- *NFκB-regulated cytokine mRNA genes levels of TNFα, IL-1β, IL-8 and IL-10 are significantly upregulated in acne-involved skin compared to uninvolved normal adjacent skin.*
- *increase in the presence of neutrophils,*
- *Inflammation is further characterised by action of active lipid mediators, such as leucotrienes (LT), prostaglandins (PG) and 15-hydroxyeicosatetraenoic acids (15-HETE).*

# *Propionibacterium acnes*

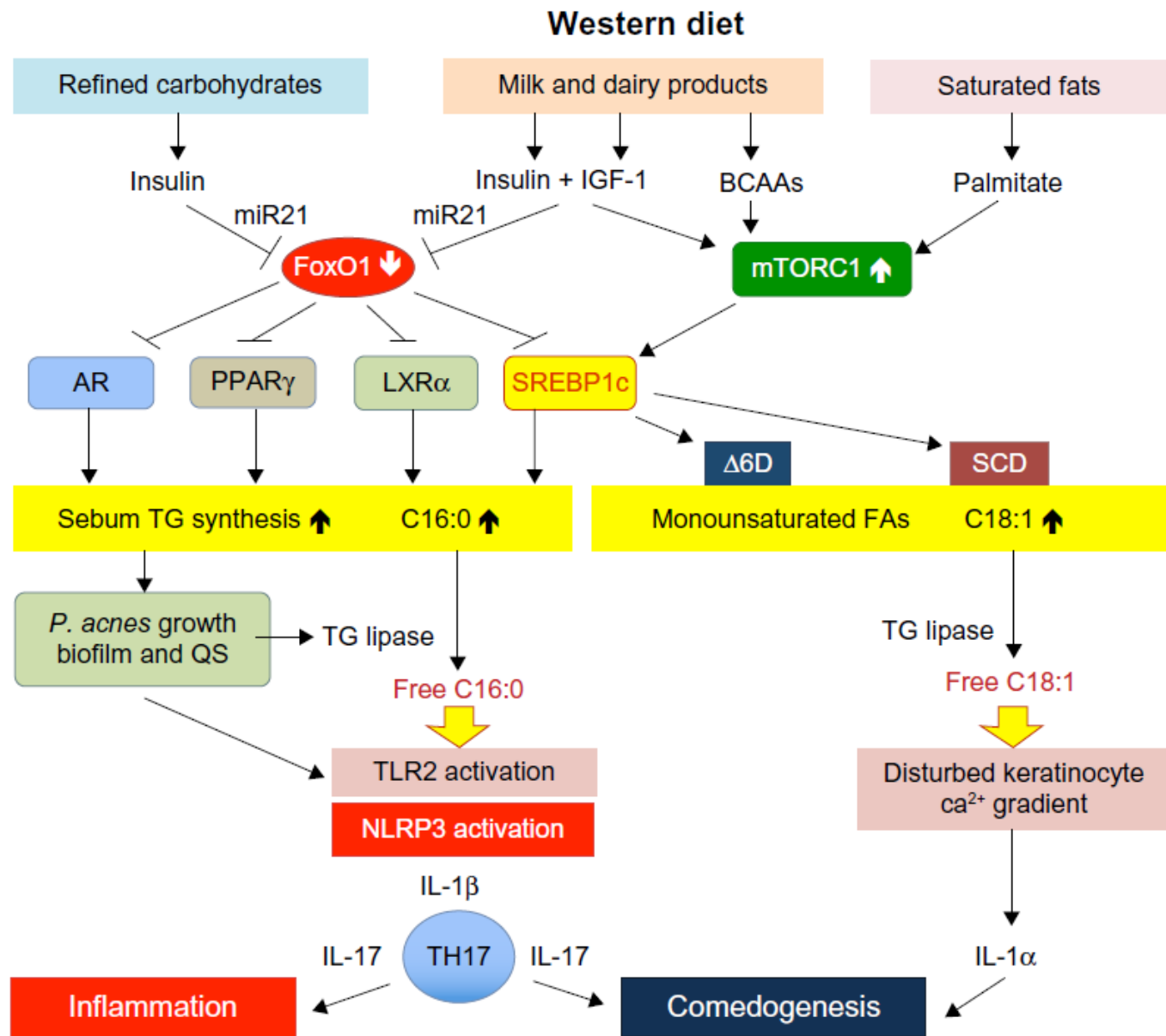


- *is a gram-positive anaerobic bacterium which with other non-pathogenic microorganisms, resides in pilosebaceous follicles.*
- *The bacteria stimulate the production of proinflammatory cytokines, including interleukins-1 $\beta$ , -8 and -12, and TNF $\alpha$ . It is known that *P. acnes*-induced cytokine production is mediated by Toll-like receptor (TLR) 2.*
- *Both cell types can be activated by *P. acnes* via toll-like receptors (TLR), CD14 and CD1 molecules.*
- *The expression of TLR2, TLR4, TLR6 and CD14 has been already documented in SZ95 sebocytes*

# Modern aspects of the pathogenesis of acne



Androgens, lipid ligands of the **peroxisome proliferation-activating receptor (PPAR)**, regulatory neuropeptides with hormonal and non-hormonal activity and environmental factors led to hyperseborrhea, epithelial hyperproliferation in the sebaceous duct and acroinfundibulum and to expression of pro-inflammatory chemokines/cytokines, which stimulate the development of comedones and inflammatory acne lesions





## ***Acne : clinica***

### ***Lesioni non infiammatorie:***

- Comedone aperto (punto nero)
- Comedone chiuso (microcisti)

### ***Lesioni infiammatorie:***

- Papule
- Pustole
- noduli

The various clinical appearances of acne vulgaris



# Global acne grading system

Location	Factor
Forehead	2
Right cheek	2
Left cheek	2
Nose	1
Chin	1
Chest and upper back	3

*Each type of lesion is given a value depending on severity: no lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4. The score for each area (Local score) is calculated using the formula: local score = factor × grade (0–4). The global score is the sum of local scores, and acne severity was graded using the global score. A score of 1–18 is considered mild; 19–30, moderate; 31–38, severe; and > 39, very severe.*

## Global Acne Assessment Scale

0	Clear. No lesions	Residual pigmentation and erythema may be seen
1	Almost clear. Almost no lesions	A few scattered open or closed comedones and very few papules
2	Mild	<i>Easily recognizable:</i> less than half of the face is involved. A few open or closed comedones and a few papules and pustules
3	Moderate	<i>More than half of the face</i> is involved. <i>Many</i> papules and pustules, many open or closed comedones. One nodule may be present
4	Severe	<i>Entire face</i> is involved, covered with many papules and pustules, open or closed comedones and rare nodules
5	Very severe	<i>Highly inflammatory acne</i> covering the face with presence of <i>nodules</i>



Grade I (mild) acne showing comedones with few inflammatory papules and pustules.

Grade	Severity	Clinical findings
I	Mild	Open and closed comedones with few inflammatory papules and pustules



Grade II (moderate) acne showing papules and pustules.

II

Moderate

Papules and pustules, mainly on face





Grade III (moderately severe) acne showing numerous large painful nodules and pustules as well as some inflamed nodules.

III

Moderately  
severe

Numerous papules and pustules,  
and occasional inflamed nodules,  
also on chest and back



Grade IV (severe) acne showing many large inflamed nodules and pustules as well as scarring.

IV

Severe

Many large, painful nodules and pustules

# Differential Diagnosis of Acne

Diagnosis	Distinguishing features
Bacterial folliculitis	Abrupt eruption; spreads with scratching or shaving; variable distribution
Drug-induced acne	Use of androgens, adrenocorticotrophic hormone, bromides, corticosteroids, oral contraceptives, iodides, isoniazid, lithium, phenytoin (Dilantin)
Hidradenitis suppurativa	Double comedo; starts as a painful boil; sinus tracts
Miliaria	“Heat rash” in response to exertion or heat exposure; nonfollicular papules, pustules, and vesicles
Perioral dermatitis	Papules and pustules confined to the chin and nasolabial folds; clear zone around the vermilion border
Pseudofolliculitis barbae	Affects curly-haired persons who regularly shave closely
Rosacea	Erythema and telangiectasias; no comedones
Seborrheic dermatitis	Greasy scales and yellow-red coalescing macules or papules

# Management of acne

## Key points

- Effective therapies for acne target one or more pathways in the pathogenesis of acne, and combination therapy gives better results than monotherapy.
- Topical therapies are the standard of care for mild to moderate acne.
- Systemic therapies are usually reserved for moderate or severe acne, with a response to oral antibiotics taking up to six weeks.
- Hormonal therapies provide effective second-line treatment in women with acne, regardless of the presence or absence of androgen excess.

Severity; clinical findings	Treatment options	
	First line	Second line
<b>Mild</b>		
Comedonal	Topical retinoid	Alternative topical retinoid Salicylic acid washes
Papular/pustular	Topical retinoid Topical antimicrobial <ul style="list-style-type: none"> <li>• benzoyl peroxide</li> <li>• clindamycin</li> <li>• erythromycin</li> </ul> Combination products	Alternative topical retinoid plus alternative topical antimicrobial Salicylic acid washes
<b>Moderate</b>		
Papular/pustular	Oral antibiotics <ul style="list-style-type: none"> <li>• tetracyclines</li> <li>• erythromycin</li> <li>• trimethoprim– sulfamethoxazole</li> </ul> Topical retinoid ± benzoyl peroxide	Alternative oral antibiotic Alternative topical retinoid Benzoyl peroxide
Nodular	Oral antibiotic Topical retinoid ± benzoyl peroxide	Oral isotretinoin Alternative oral antibiotic Alternative topical retinoid Benzoyl peroxide
<b>Severe</b>	Oral isotretinoin	High-dose oral antibiotic Topical retinoid (also maintenance therapy) Benzoyl peroxide

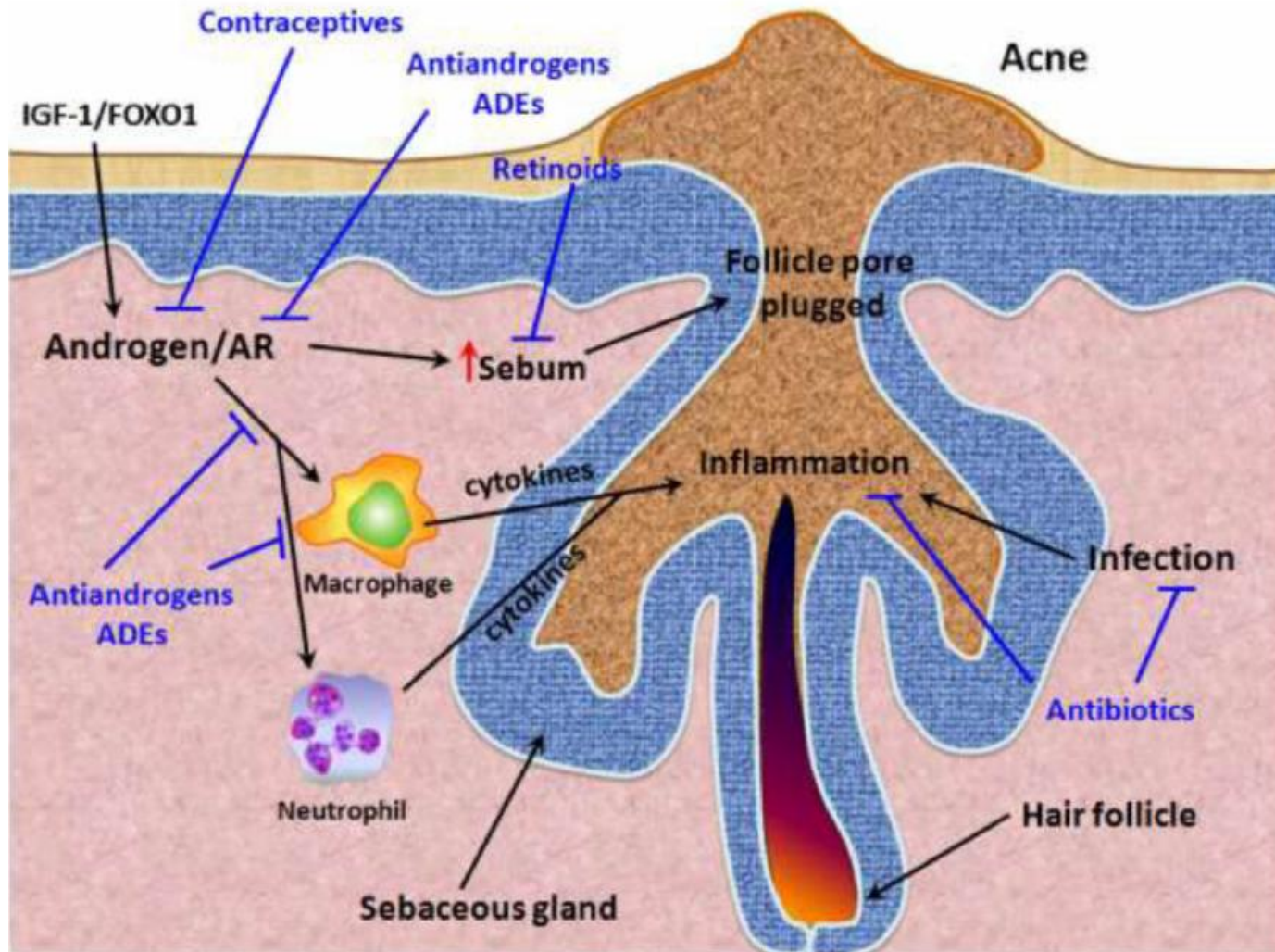
*La cura dell'acne prevede l'impiego di più farmaci in modo da poter agire sulle diverse componenti della malattia: comedonica (retinoidi), infiammatoria (benzoil perossido), batterica (antibiotici)*

- *Benzoile perossido idrato (Benzac, Benzac clean, Panoxyl, Reloxyl)*
- *Isotretinoina (Aisoskin, Isoriac, Isotretinoin, Isotrex gel, Roaccutan)*

Antibiotic, dose	Notes
Tetracycline 250–500 mg twice daily	<ul style="list-style-type: none"> <li>• Inexpensive</li> <li>• Contraindicated in pregnant women or in children under nine years of age</li> <li>• Chelated by antacids and milk; to be taken on empty stomach</li> </ul>
Minocycline 50–200 mg daily	<ul style="list-style-type: none"> <li>• Can be taken with food</li> <li>• Contraindicated in pregnant women or in children under nine years of age</li> <li>• Adverse reactions: dizziness, pigment changes, hepatitis, lupus-like reactions</li> </ul>
Doxycycline 100–200 mg daily	<ul style="list-style-type: none"> <li>• Can be taken with food</li> <li>• Acceptable for use in patients with renal failure</li> <li>• Contraindicated in pregnant women or in children under nine years of age</li> <li>• Adverse reactions: gastrointestinal upset; phototoxicity (greatest of all tetracyclines)</li> </ul>
Erythromycin 500 mg twice daily	<ul style="list-style-type: none"> <li>• Safe in pregnant women and children</li> <li>• Adverse reaction: may cause gastrointestinal upset</li> <li>• 42% of patients may show resistance to <i>Propionibacterium acnes</i><sup>18</sup></li> </ul>
Trimethoprim/ sulfamethoxazole 80/400 mg or 160/800 mg four times a day	<ul style="list-style-type: none"> <li>• Useful in patients resistant to other antibiotics</li> <li>• Adverse reactions: 3%–4% of patients experience rash,<sup>21</sup> risk of serious skin reactions, such as Stevens–Johnson syndrome</li> </ul>



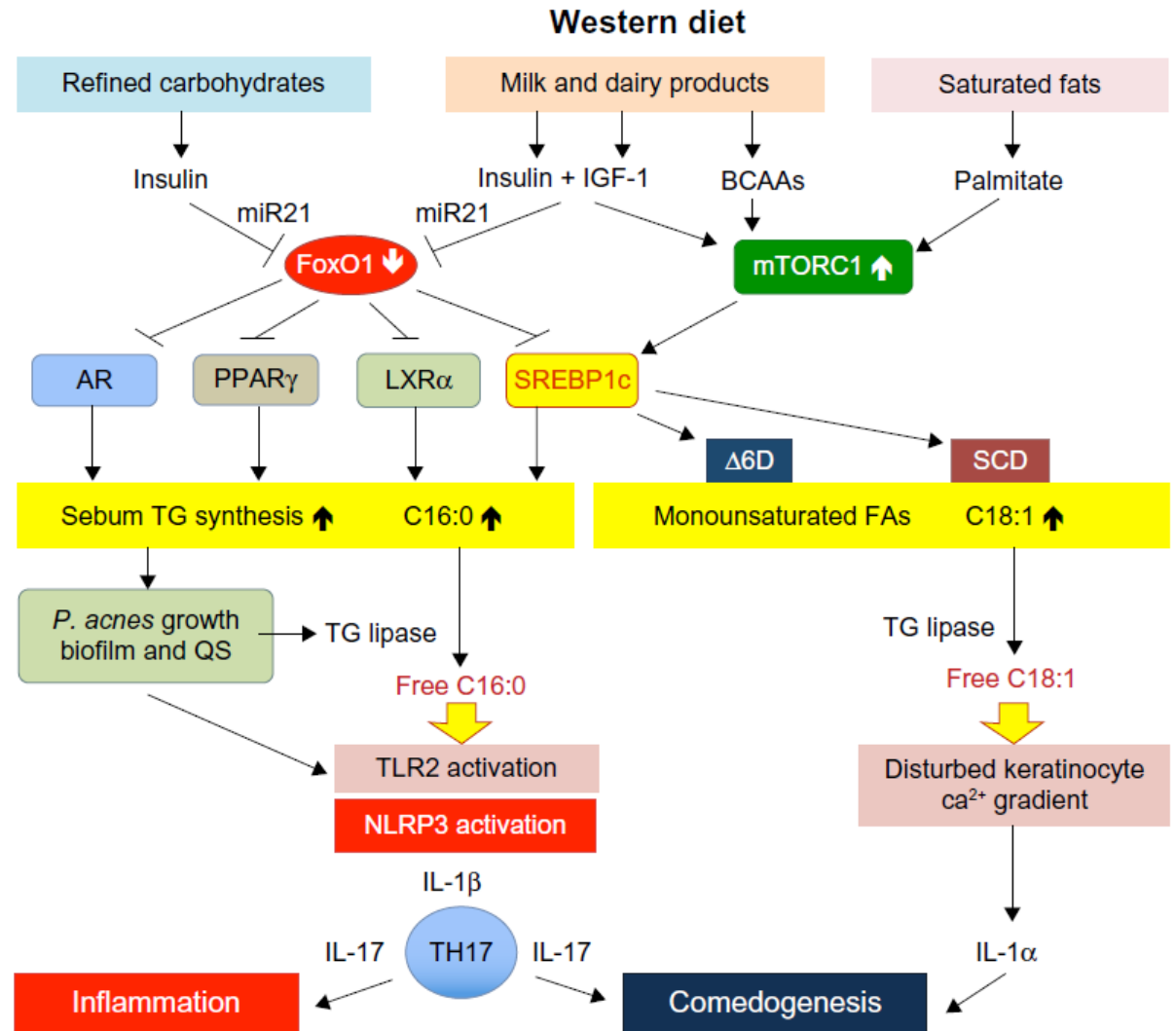
# The Role of Androgen and Androgen Receptor in the Skin Related Disorders





# Linking diet to acne metabolomics, inflammation, and comedogenesis: an update

IGF-1, insulin-like growth factor 1;  
 BCAAs, branched-chain amino acids;  
 miR21, microRNA-21;  
 FoxO1, forkhead box class O1;  
 mTORC1, mechanistic target of rapamycin complex 1;  
 AR, androgen receptor;  
 PPAR $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ;  
 LXR $\alpha$ , liver X receptor- $\alpha$ ;  
 SREBP1c, sterol response element binding protein 1c;  
 $\Delta$ 6D,  $\Delta$ 6-desaturase;  
 SCD, stearoyl-CoA desaturase;  
 TG, triglyceride;  
*P. acnes*, *Propionibacterium acnes*;  
 QS, quorum sensing;  
 C16:0, palmitic acid; C18:1, oleic acid;  
 TLR2, toll-like receptor 2;  
 NLRP3, Nod-like receptor family, pyrin domain containing 3 inflammasome;  
 IL-1 $\beta$ , interleukin-1 $\beta$ ;  
 Th17, Th17 T-cell; IL-17, interleukin-17,  
 IL-1 $\alpha$ , interleukin-1 $\alpha$ .



## Acneigenic food components of Western diet

Nutrients	Metabolic and nutrigenomic effects	Sources
Hyperglycemic carbohydrates	Postprandial hyperinsulinemia	Sugar
	Insulin-mediated hepatic IGF-I synthesis	Sweets
	Reduction of IGFBP3	Soft drinks
	Increased bioavailability of free circulating IGF-I	Pizza
	Reduction of SHBG	Pasta
	Increased bioavailability of free circulating testosterone	Wheat bread
	Reduced nuclear activity of FoxO1	Wheat rolls
	Increased expression of sebocyte SREBP-1c	Cornflakes
Milk and dairy products	Activation of mTORC1	
	Glucose-mediated microRNA-21 expression	
	Postprandial hyperinsulinemia	Whole and skim milk
	Increased levels of circulating IGF-I	Pasteurized fresh milk
	Leucine-mediated activation of mTORC1	Yogurt
	Glutamine-mediated activation of mTORC1	Ice cream
Saturated fats	Palmitate-mediated activation of mTORC1	Whey and casein supplements
	Palmitate-mediated activation of mTORC1	Cheese
	Milk-microRNA-21-mediated proliferation and inflammation	Butter
<i>Trans</i> -fats	Palmitate-driven inflammasome activation	Cream
	Possible mTORC1 activation	Fast food
	Proinflammatory signaling	French fries

IGF-1, insulin-like growth factor 1; IGFBP3, IGF binding protein 3; SHBG, sex hormone binding globulin; FoxO1, forkhead box O1; SREBP-1c, sterol response element binding protein 1c; mTORC1, mechanistic target of rapamycin complex 1.

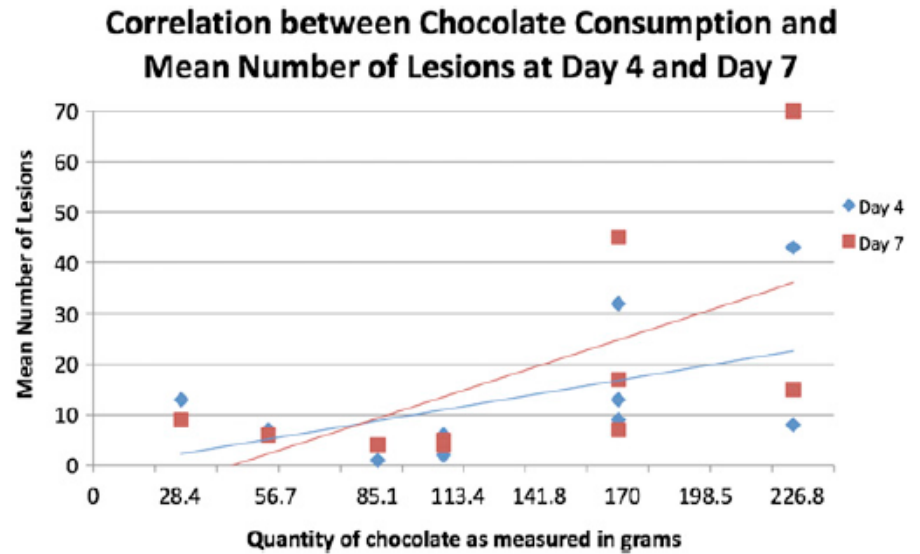
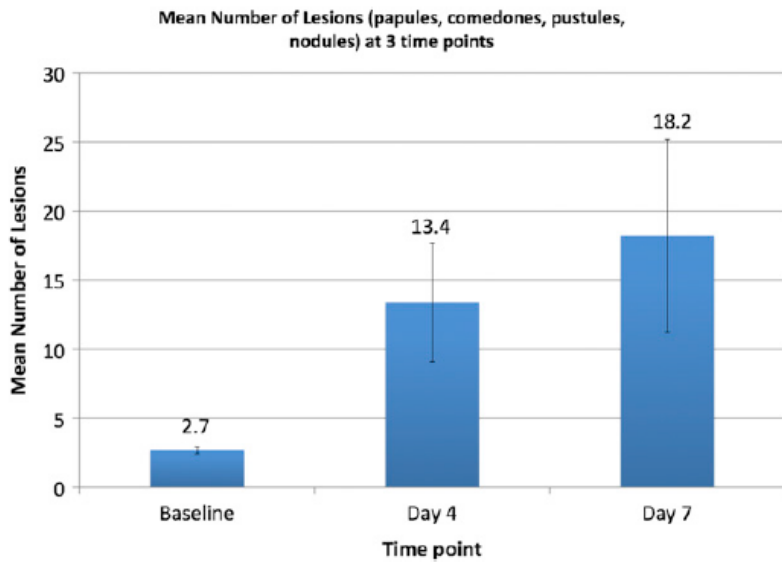
## ***Dietary modifications for patients with acne with recommendations and the associated level of evidence***

Dietary modification	Recommendation	Level of evidence
Low glycemic index/load diet	Yes	IB
Milk restriction	Insufficient data for conclusive recommendation	III

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from  $\geq 1$  randomized controlled trial; level IIA evidence includes evidence from  $\geq 1$  controlled study without randomization; level IIB evidence includes evidence from  $\geq 1$  other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.*

*Multiple randomized controlled trials with biochemical and histopathologic evidence support the benefit of a low glycemic index/load diet for acne patients  
While observational studies suggest that frequent milk consumption imparts a higher risk of acne, randomized controlled trials are necessary before dietary recommendations can be made*

# Exacerbation of facial acne vulgaris after consuming pure chocolate



## **The constellation of dietary factors in adolescent acne: a semantic connectivity map approach**

*High-GL diet is implicated in the aetiology of acne predominately through the induction of hyperinsulinaemia and consequent increase in insulin and IGF-1 concentrations.*

*The acne-promoting or aggravating mechanisms of milk and dairy products are not well understood and seem to be multifactorial.*

*Similar to high-GL foods, milk consumption increases insulin and IGF-1 concentrations.*

*It has been shown that a diet rich in n-3 polyunsaturated fatty acids, including fish, may suppress inflammatory cytokine production, thus decreasing acne*

# Acne-Related Quality of Life Among Female Adults of Different Races/Ethnicities

## Acne-specific Quality of Life (Acne-QoL)

### Self Perception

- Feel unattractive
- Feel embarrassed
- Feel self-conscious
- Dissatisfied with self appearance
- Self-confidence negatively affected

### Role-Emotional

- Feel upset
- Feel annoyed about time spent treating face
- Worried about not looking your best
- Worried about medication not working fast enough
- Feel bothered about needing to have medication/cover-up available

### Role-Social

- Worried about meeting new people
- Worried about going out in public
- Problem with socializing
- Problem with interacting with the opposite sex (or same sex if gay or lesbian)

### Acne Symptoms

- Bumps on face
- Bumps full of pus
- Scabbing from acne
- Worried about scarring from acne
- Oily skin

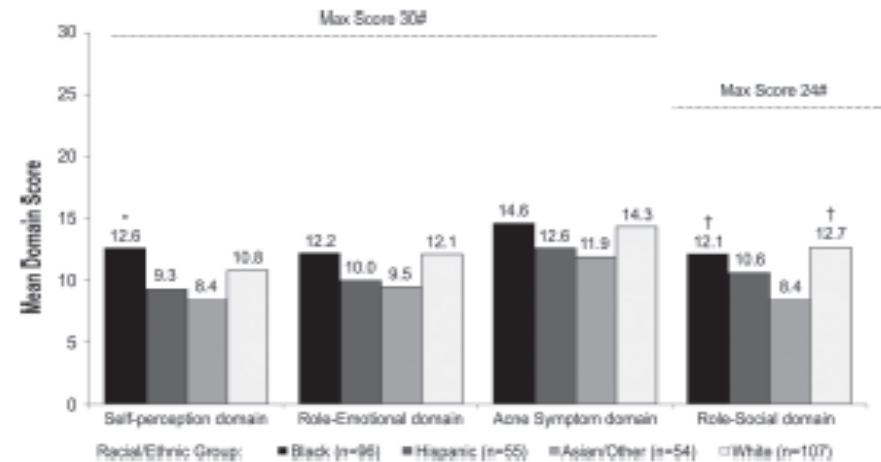
## Patient Health Questionnaire (PHQ-4)

### Anxiety

- Feel nervous, anxious, or on edge
- Not able to stop or control worrying

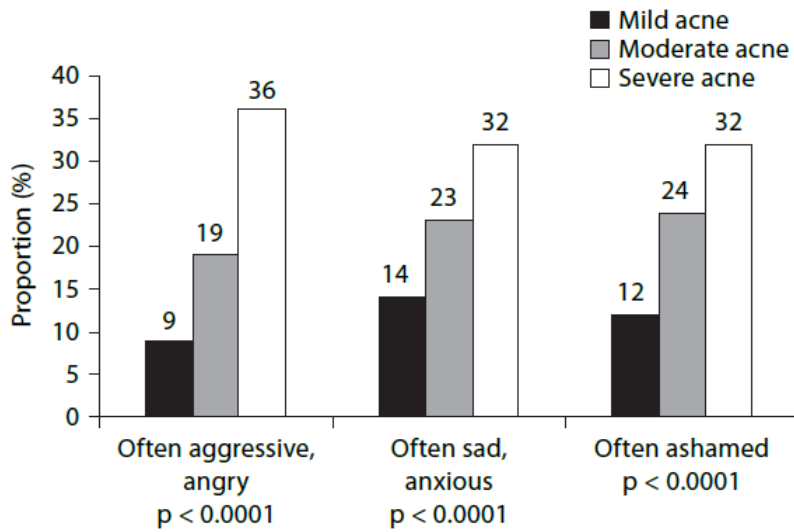
### Depression

- Little interest or pleasure in doing things
- Feel down, depressed, or hopeless

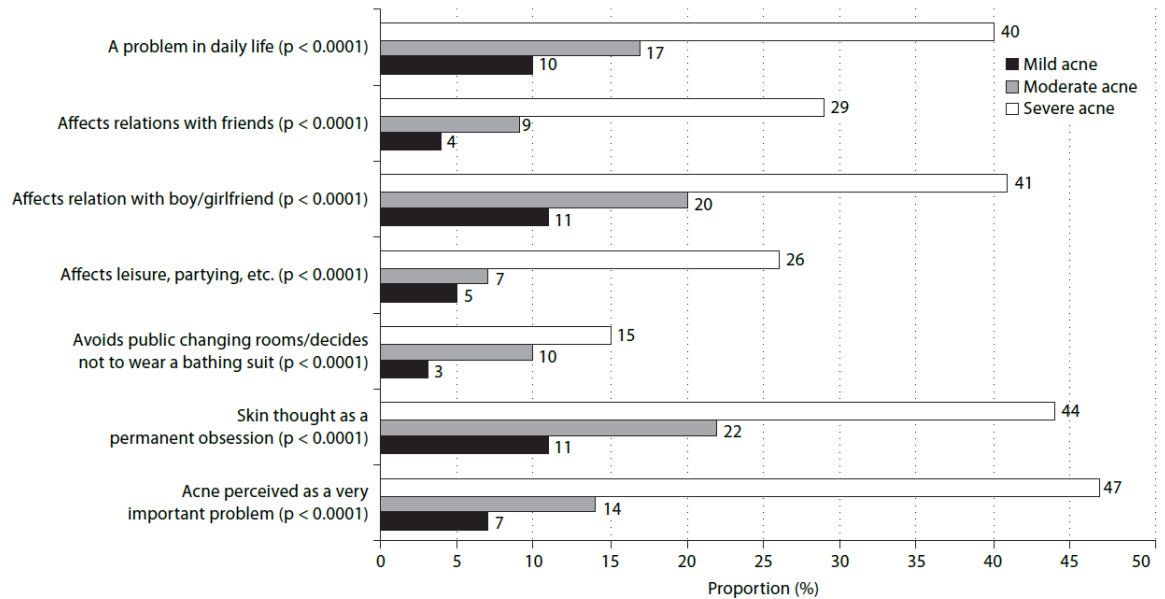
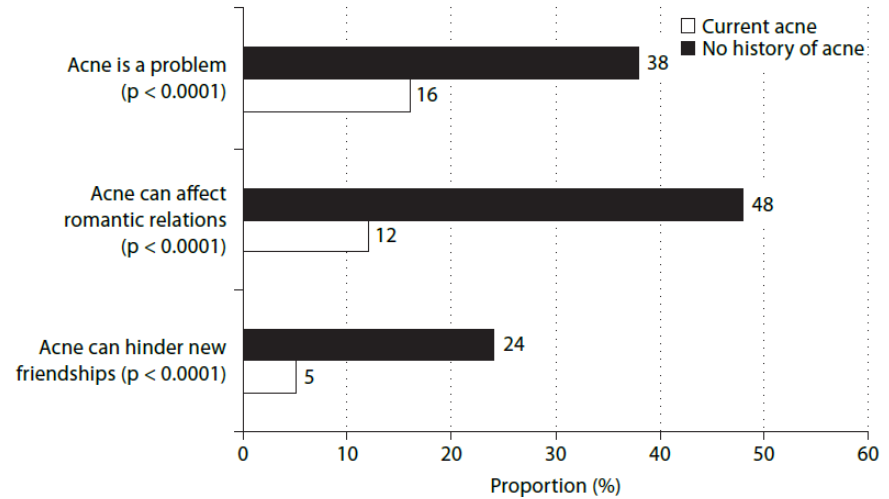


Acne-Specific Quality of Life Questionnaire domain scores by racial/ethnic group; N = 312. \*Analysis of variance (ANOVA) comparing Black versus Asian/Other,  $p = .05$ ; †ANOVA comparing Black versus Asian/other,  $p = .06$ , and White versus Asian/other,  $p < .05$ ; #higher scores indicate better health-related quality of life.

Because of your acne spots, have you been... ?



n = 711



# Acne vulgaris

## Summary points

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Acne is a multifactorial disease which, although not life threatening, has profound effects on patients

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The microcomedo is the primary lesion in acne

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Reduction of comedones and *Propionibacterium acnes* is the main aim of treatment

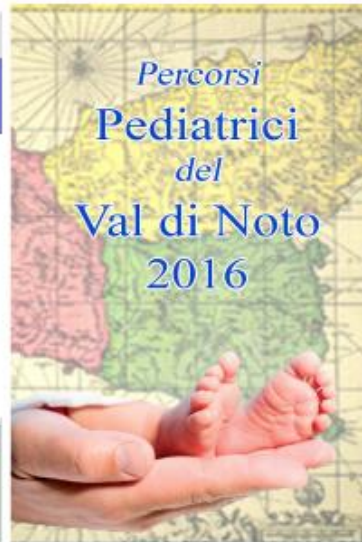
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Most effective acne regimens treat inflammatory and comedonal acne lesions with a combination of antibacterial and retinoid drugs





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***Grazie per l'attenzione***